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A Meta-analysis of the Association of Estimated GFR, Albuminuria, Age, Race, and Sex With Acute Kidney Injury

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Abstract

Background—Acute kidney injury (AKI) is a serious global public health problem. We aimed to quantify the risk of AKI associated with estimated glomerular filtration rate (eGFR), albuminuria (albumin-creatinine ratio [ACR]), age, sex, and race (African American and Caucasian).

Study Design—Collaborative meta-analysis.

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Setting & Population—8 general population cohorts (1,285,049 participants) and 5 chronic kidney disease (CKD) cohorts (79,519 participants).

Selection Criteria for Studies—Available eGFR, ACR, and 50 AKI events.

Predictors—Age, sex, race, eGFR, urine ACR, and interactions.

Outcome—Hospitalized with or for AKI, using Cox proportional hazards models to estimate HRs of AKI and random effects meta-analysis to pool results.

Results—16,480 (1.3%) general population cohort participants had AKI over a mean follow-up of 4 years; 2,087 (2.6%) CKD participants had AKI over mean follow-up of 1 year. Lower eGFR and higher ACR were strongly associated with AKI. Compared with eGFR 80 ml/min/1.73 m², the adjusted HR of AKI at eGFR 45 ml/min/1.73 m² was 3.35 (95% CI, 2.75–4.07). Compared with ACR 5 mg/g, the risk of AKI at ACR 300 mg/g was 2.73 (95% CI, 2.18–3.43). Older age was associated with higher risk of AKI, but this effect was attenuated in lower eGFR or higher ACR. Male sex was associated with higher risk of AKI, with a slight attenuation in lower eGFR but not in higher ACR. African Americans had higher AKI risk at higher levels of eGFR and most levels of ACR.

Limitations—Only 2 general population cohorts could contribute to analyses by race; AKI identified by diagnostic code.

Conclusions—Reduced eGFR and increased ACR are consistent, strong risk factors for AKI whereas the associations of AKI with age, sex, and race may be weaker in more advanced stages of CKD.

Keywords

estimated glomerular filtration rate (eGFR); renal function; albuminuria; albumin-creatinine ratio (ACR); proteinuria; age; race/ethnicity; sex; acute kidney injury (AKI); acute renal failure (ARF); Chronic Kidney Disease Prognosis Consortium; meta-analysis

Acute kidney injury (AKI) is increasingly recognized as a serious problem in global public health.¹ Although estimates of AKI incidence in the general population are sparse, AKI occurs in 3.2%–9.6% of hospital admissions^{2,3} and 2.1%–22.1% of prevalent intensive care unit patients⁴ worldwide. Furthermore, AKI is associated with substantial morbidity, including prolonged hospital stay, end-stage renal disease (ESRD), earlier stages of chronic kidney disease (CKD), and short- and long-term mortality.^{3,5,6}

Certain patient characteristics may predispose to AKI. Chronic kidney disease, assessed as decreased estimated glomerular filtration rate (eGFR) or elevated albuminuria, has been linked to increased AKI risk.^{7–10} Similarly, older age, male sex, and African American race have been associated with higher risk of AKI.^{11–13} The generalizability of existing studies investigating demographic risk factors is limited, with most estimates derived in single cohorts. In addition, little attention has been paid to how demographic associations may vary over the spectrum of kidney function. Thus, the objectives of this study were to evaluate the associations of eGFR and albuminuria with AKI in a large global consortium of studies, as well as to investigate the relative importance of age, sex, and race across the full range of eGFR and albuminuria.

METHODS

Design Overview

Study data were obtained by the Chronic Kidney Disease Prognosis Consortium (CKD-PC) for meta-analysis as previously described.^{10,14–17} Cohorts with baseline measures of eGFR and albuminuria, at least 1000 participants (not applied to cohorts preferentially enrolling persons with eGFR <60 ml/min/1.73 m²), and at least 50 AKI events were eligible for inclusion. This study was approved for use of de-identified data by the Institutional Review Board at the Johns Hopkins University Bloomberg School of Public Health (IRB number: 3324).

Settings and Participants

Thirteen studies met eligibility criteria. All cohorts were included in analyses of AKI incidence and the risk associated with eGFR, but only those with measured risk factors or populations relevant for the comparison of interest were included in analyses of ACR, age, sex, and race (e.g., studies measuring proteinuria by dipstick were not included in continuous analyses of ACR, and the all-male Uppsala Longitudinal Study of Adult Men [ULSAM] was not included in the analysis by sex). For the present study, only participants with baseline eGFR >15 ml/min/1.73 m² were included, and participating studies were categorized as either general population or CKD cohorts, reflecting the distribution of eGFR and ACR.

Interventions

The eGFR was calculated using creatinine concentrations (standardized when possible to isotope dilution mass spectrometry) and the 2009 CKD Epidemiology Collaboration (CKD-EPI) creatinine equation.¹⁸ The preferred measure of albuminuria was urine albumin-creatinine ratio (ACR); however, cohorts with quantitative dipstick protein were also included in analyses of eGFR, adjusting for ordinal category of dipstick results. In categorical analyses, dipstick test results of negative, trace, 1+, and 2+ were considered equivalent to an ACR of <10, 10–29, 30–299, and ≥300 mg/g, respectively,^{19,20} and the groups of ACR <30, 30–299, and ≥300 mg/g were referred to as no albuminuria, moderately-increased albuminuria, and severely-increased albuminuria.²¹ Age, sex, and race were self-reported, with the former categorized as 18–54, 55–64, 65–74, and ≥75 years in interaction analysis, and the latter categorized as African American and non-African American (95% of non-African American participants were Caucasian) when used as a covariate in adjustment and African American and Caucasian when used as a covariate in the interaction analysis.

Outcomes and Follow-up

The primary outcome was diagnostic code-defined AKI, determined as an *International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM)* code of 584.x or an *International Classification of Disease, 10th Revision, Clinical Modification (ICD-10-CM)* code of N17.x associated with a hospitalization. These codes have been validated previously in the United States, Israel, and Canada, with lower sensitivity (range, 17%–

80%) but high specificity (range, 96%–100%).^{22–24} Sensitivity was generally higher for more severe disease.²⁵ Follow-up was censored at the development of ESRD, death, or loss-to-follow-up.

Statistical Analysis

Analyses were performed by two-stage meta-analysis. At the first stage, each study was analyzed individually, using all participants aged 18 years or older with baseline eGFR and albuminuria. Missing values for covariates other than age, sex, and race were estimated using mean imputation. Variables missing in >50% of the cohort were not included as covariates (Item S1, available as online supplementary material). Cox proportional hazards models were fitted on eGFR linear splines (knots at 30, 45, 60, 75, 90, and 105 ml/min/1.73 m²), log-transformed ACR splines (knots at 10, 30, and 300 mg/g for general population cohorts; knots at 30, 300, and 1000 mg/g for CKD cohorts), age, sex, race, BMI, smoking, diabetes, systolic blood pressure, history of cardiovascular disease, and total cholesterol. Due to small sample size in the analyses by race, the upper and lower knots in eGFR were omitted for these models. The overall relationship between eGFR and AKI was then determined, calculating the hazard ratios (HRs) at each 1-ml/min/1.73 m² increment. Next, the interactions between eGFR and each risk factor (age, sex, or race) were determined by including the eGFR-risk factor product term in the Cox model. For cohorts with ACR, a similar method was used to estimate the risk associated with ACR and the interactions between ACR and each risk factor. For analyses of general population cohorts, a reference eGFR of 80 ml/min/1.73 m² and ACR of 5 mg/g were used, as described previously.²⁶ For analyses of CKD cohorts, a reference eGFR of 50 ml/min/1.73 m² and ACR of 50 mg/g were used. Heterogeneity of effects was investigated using the *I*² statistic.

At the second stage, estimates from each cohort were pooled using a random-effects model, with each study receiving a weight corresponding to the inverse of the variance of each spline coefficient. Pointwise interaction was estimated as the ratio of HRs in each age, sex, or race category compared with the reference category (age 55–64 years, male sex, and Caucasian race, respectively) at each 1-ml/min/1.73 m² increment of eGFR or 8% increment in ACR. The adjusted incidence rates at eGFR 80 ml/min/1.73 m² and ACR 5 mg/g were estimated as the weighted-average study-specific incidence rates for the reference category of each risk factor (age 55–64 years, male sex, and Caucasian race) as previously described.²⁶ This value was treated as a fixed reference point, and the adjusted incidence rate at each increment of eGFR and ACR was estimated as the product of the fixed reference and the meta-analyzed HRs. Finally, pooled HRs in 7 categories of eGFR (15–29, 30–44, 45–59, 60–74, 75–89, 90–104, 105 ml/min/1.73 m²) and 4 categories of ACR (<10, 10–29, 30–299, 300 mg/g) were compared across age, race, and sex categories to assess overall interactions. Multiplicative interactions with p-values <0.05 were considered significant. All analyses were performed using Stata version 13.1 MP (StataCorp LP).

RESULTS

Baseline Characteristics

Thirteen cohorts from 8 different countries comprising 1,364,568 participants met eligibility criteria (Table 1 and Table S1). The 8 general population cohorts had 1,285,049 participants and 16,480 cases of AKI during a mean follow-up of 4 years. Among these cohorts, average eGFR was 90 ml/min/1.73 m², and 7% had ACR ≥ 30 mg/g (or dipstick proteinuria 1+). The 5 CKD cohorts had 79,519 participants with 2,087 cases of AKI over a mean follow-up of 1 year. Among the CKD cohorts, average eGFR was 63 ml/min/1.73 m², and 55% had ACR ≥ 30 mg/g (or dipstick proteinuria 1+).

Participants with AKI had lower average eGFR and a greater likelihood of ACR ≥ 30 mg/g than those without AKI in all individual cohorts. In the general population cohorts, persons with AKI were older, more often male, and more often African American. These associations were not present in the CKD cohorts, where there was more between-study heterogeneity in the crude associations of age, sex, and race with AKI.

Overall Associations of eGFR and ACR With AKI

In pooled meta-analysis of general population cohorts, the relationship between eGFR and AKI risk was nearly linear between eGFR 90 and 15 ml/min/1.73 m² (Figure 1, panel A). For example, at eGFR 45 ml/min/1.73 m², the risk of AKI was consistently elevated compared with eGFR 80 ml/min/1.73 m² (pooled HR, 3.35; 95% CI, 2.75–4.07; p<0.001), albeit with some variation in effect size across cohorts (Figure S1, panel A). Higher levels of ACR were also nearly linearly associated with higher AKI risk (Figure 1, panel B), with most cohorts showing elevated risk at ACR 300 mg/g compared with ACR 5 mg/g (pooled HR, 2.73; 95% CI, 2.18–3.43; p<0.001) (Figure S1, panel B). The presence of moderately- or severely-increased albuminuria was associated with higher AKI risk across the range of eGFR (Figure 1, panel C), with a small but significant attenuation in effect at lower eGFR (Figure S1, panels C and D). In categorical analyses in the general population cohorts, risk for AKI was significantly higher in most categories defined by lower eGFR or higher ACR (Figure 1, panel D). The relationships of eGFR and ACR with AKI risk were similar in the CKD cohorts (Figure S2).

Associations by and of Age With AKI

In the general population cohorts, lower eGFR and higher ACR were associated with higher AKI risk in all age groups (Figure 2, panels A and C). Older age itself was associated with higher risk for AKI at eGFR 80 ml/min/1.73 m²; at eGFR < 60 ml/min/1.73 m², adjusted HRs in each age category overlapped, with minimal variation across studies (overall interaction compared with reference age 55–64 years: p=0.001 for ages 18–54, p<0.001 for age 65–74, and p<0.001 for age 75 years and older) (Figures S3 and S4). Similarly, the association of age and AKI was attenuated at higher levels of ACR (overall interaction compared with reference age 55–64 years: p=0.1 for age 18–54, p=0.07 for age 65–74, and p=0.05 for age 75 years and older) (Figures S5 and S6). In categorical analysis in the general population cohorts, the HRs associated with lower eGFR and higher ACR were smaller in older age groups (Table S2). In CKD cohorts, there was little difference by age in AKI risk

across the range of eGFR and ACR, consistent with the observed attenuation in lower eGFR and higher ACR in general population studies (Figure S7). On the absolute scale using general population estimates, the adjusted incidence rate of AKI increased sharply at eGFR < 60 ml/min/1.73 m² and nearly linearly with a fold-increase in ACR. Older age groups had higher rates of AKI at eGFR 80 ml/min/1.73 m² and ACR 5 mg/g, but this was not observed at eGFR 45 ml/min/1.73 m² or ACR > 300 mg/g (Figure 2, panels B and D).

Associations by and of Sex With AKI

In the general population cohorts, lower eGFR and higher ACR were associated with higher AKI risk in both men and women (Figure 3, panel A and C). Here, men had higher risk of AKI at all levels of eGFR (Figure S8 and S9) and ACR (Figures S10 and S11), although this appeared attenuated at lower eGFR but not for higher ACR (overall interaction: $p < 0.001$ for eGFR, $p = 0.9$ for ACR). In categorical analysis of the general population cohorts, the association of categories defined by lower eGFR or higher ACR was slightly stronger among women (Table S3). In CKD cohorts, male sex was associated with higher AKI risk at eGFR > 40 ml/min/1.73 m² and ACR < 300 mg/g (Figure S12). On the absolute scale using general population cohort estimates, the adjusted incidence rates of AKI increased with eGFR < 60 ml/min/1.73 m² and linearly with a fold-increase in ACR, and men had higher adjusted incidence rates than women at all levels of eGFR and ACR (Figure 3, panels B and D).

Associations by and of Race With AKI

Few studies had sufficient numbers of AKI events in both African American and white participants to allow analyses by race (2 in the general population cohorts, and 2 in the CKD cohorts), limiting power (Figures S13–S16). The overall association of lower eGFR and higher ACR with higher AKI risk persisted by category of race. African Americans had higher risk of AKI than whites at higher eGFR in the general population cohorts; however, CIs overlapped at lower eGFR (Figure 4, panel A). In contrast, African Americans had higher AKI risk than whites in the upper but not lower range of ACR (Figure 4, panel C). In categorical analyses in the general population cohorts, there was little evidence to suggest an interaction of eGFR or ACR with race in risk for AKI (Table S4), and results of analyses in CKD cohorts were similar (Figure S16). On the absolute scale using general population estimates, African Americans had higher absolute risk of AKI at eGFR 80 and 45 ml/min/1.73 m² as well as at ACR 5 and 300 mg/g (Figure 4, panel B and D; Fig S17).

DISCUSSION

This collaborative meta-analysis of over 1 million participants from 8 countries treated in a variety of settings demonstrates that low eGFR and high albuminuria are robust risk factors for AKI. The associations of lower eGFR and higher albuminuria with AKI were consistent in nearly all general population and CKD cohorts, and within categories of age, sex, and race. Older age, male sex, and African American race were associated with increased risk of AKI in the normal range of kidney function, but the associations were attenuated in the lower range of eGFR (for older age and male sex) and higher range of ACR (for older age).

These results suggest the primacy of low eGFR and high ACR in AKI risk stratification—an observation that could guide preventative efforts.

The present study expands on previous work demonstrating associations between kidney measures and AKI risk. Earlier population-based studies (including a meta-analysis of 4 cohorts by the CKD Prognosis Consortium) linked AKI to lower eGFR as assessed by the Modification of Diet in Renal Disease (MDRD) Study equation.^{8–11} The current meta-analysis evaluates this relationship among 1 million participants from 13 cohorts and 8 countries using the CKD-EPI equation to estimate GFR—an equation with improved performance over the MDRD Study equation, particularly among younger people.¹⁸ Furthermore, we show that the eGFR-AKI relationship, as well as that between albuminuria and AKI, is robust across study type (including CKD versus general population cohort) and location, and subgroups of age, sex, and race.

There are several possible mechanisms for the association of kidney function markers and AKI. Iatrogenic complications occur more commonly in persons with reduced eGFR.²⁷ Lower eGFR is a risk factor for hospitalization, which is itself a risk factor for AKI.¹³ In addition, many medications requiring dose adjustment at lower eGFR have been implicated as potential precipitants of AKI. With respect to the association between albuminuria and AKI, some postulate that persons with albuminuria have chronic proximal tubular stress in the setting of maximal albumin reclamation, and thus are predisposed to proximal tubular injury.²⁸ The association between albuminuria and AKI, while previously demonstrated, is likely under-recognized by clinicians, and might represent a major target for AKI prevention campaigns. Improvements in AKI risk assessment through routine testing of albuminuria prior to surgery or iodinated contrast exposure might result in reductions in AKI incidence in these settings.

An interesting finding from our study is the strong association of older age with AKI in the absence but not presence of CKD. Although older age has been previously implicated as a risk factor for AKI, including numerous population-based studies and surgical cohorts, to our knowledge it has not been examined over the entire spectrum of kidney function. Even with normal kidney function, older persons are hospitalized,²⁹ undergo surgery,³⁰ and develop cancer³¹ more often than younger persons, and they tend to take more medications,^{32,33} increasing the possibility of iatrogenic events.³⁴ Older persons have higher rates of medical encounters than younger persons, at least on average, and thus an AKI event in an older person may be more likely to be identified.²⁹ Finally, the sensitivity of AKI-related diagnostic codes may be higher in older persons compared with younger persons.²⁵ However, while the latter two points could explain the risk association of older age and AKI, the shape of the association between eGFR and AKI risk within age groups should be accurate in the absence of differential association by kidney measures.

Our study also suggests that male sex and African American race are independent risk factors for AKI, consistent with unadjusted analyses from the US Renal Data System (USRDS).¹² In the USRDS-reported Medicare (age ≥66 years), Truven Health MarketScan (age <65 years) and Clinformatics (age <65 years) populations, men made up 47%, 60%, and 61% of the cases of AKI, respectively, although these proportions were not adjusted for

the sex distribution in the underlying population. Similarly, rates of AKI in Medicare patients were consistently higher among those of black/African-American race. Disparities in income and health insurance may partially explain AKI disparities by race,¹³ but it is unlikely that a similar explanation applies to the disparities by sex. Men face greater risk of cardiovascular events, and treatment for such events tends to be more aggressive in men than women,³⁵ with greater use of angiography, a common proximate cause of AKI. Alternatively, prostate cancer is one of the most common cancers among men, with an estimated 15.3% of men expected to be diagnosed during their lifetime;³⁶ both prostate cancer and its treatment are associated with AKI.³⁷

There are certain strengths to this study. To our knowledge, it is the largest study to date to examine the association of eGFR, ACR, and AKI. The study population includes more than 1 million participants with eGFR across the full spectrum of kidney function, with representation from 13 cohorts and 8 countries. The associations between eGFR, ACR and AKI were robust across individual cohorts as well as within categories of age, race, and sex. Analyses were carried out in a uniform manner with adjustment for major risk factors; interactions between kidney function and age, sex, and race were assessed on both the multiplicative and additive scales.

On the other hand, AKI was identified by diagnostic code only, a method which is highly specific but relatively insensitive.²² Diagnostic codes have been validated in some but not all cohorts, and it is possible that validity varies by baseline CKD status, demographic factors, or cohort setting, with the latter explaining some of the heterogeneity between cohorts. However, it is reassuring that relationships were qualitatively similar across cohorts and between type of cohort. Because no measures of hospitalized creatinine or the use of dialysis were available, stratification by AKI severity was not possible. It is likely that diagnostic codes capture a more severe phenotype of AKI; thus, our results may not be generalizable to smaller changes in serum creatinine. Cause of AKI was not documented; thus, differentiation of potentially preventable etiologies of AKI (such as contrast-induced AKI) was not possible. Only two general population cohorts could contribute to analyses examining the risk of AKI by race; the cohorts with African Americans were US-based and thus results may not be generalizable to other countries. Finally, the random effects models used in meta-analysis are appropriately conservative but generally yield wider CIs than analyses done with a single cohort of comparable size.

Better methods for risk stratification may be critical in reducing the worldwide incidence of AKI. Although AKI is a general term encompassing a wide range of clinical entities and disease severity,³⁸ epidemiologic evidence has linked even mild, reversible changes in serum creatinine to adverse outcomes.^{39,40} Other than supportive care, there is no effective treatment for AKI; thus, risk stratification based on inherent susceptibilities may be paramount in guiding preventative strategies.⁴¹ For example, a recent review recommended universal preoperative AKI risk assessment, with subsequent avoidance of nephrotoxins and optimization of intraoperative hemodynamics in those patients categorized as high risk.⁴² Furthermore, although available interventions are limited at present, accurate assessment of AKI risk is fundamental to the design of adequately powered clinical trials.

In conclusion, the present study demonstrates that measures of kidney function—namely, eGFR and ACR—were strongly and robustly associated with AKI risk across a wide range of settings. Although older age and male sex were also associated with AKI, these associations were attenuated in the presence of CKD. Acute kidney injury risk stratification by kidney measures may be more useful than stratification by age, sex, or race.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Appendix

Supplementary Material

Table S1: Characteristics of participating cohorts.

Table S2: Adjusted HRs of AKI by category of eGFR and albuminuria across age among general population cohorts.

Table S3: Adjusted HRs of AKI by category of eGFR and albuminuria across sex among general population cohorts.

Table S4: Adjusted HRs of AKI by category of eGFR and albuminuria across race among general population cohorts.

Figure S1: Adjusted HRs of AKI in general population cohorts.

Figure S2: Adjusted HRs of AKI in CKD cohorts by level of eGFR and ACR.

Figure S3: Forest plot of general population cohorts: HRs of AKI by age category; age 55–64, eGFR 80 as reference.

Figure S4: Forest plot of general population cohorts: HRs of AKI at eGFR 45 by age category; age 55–64, eGFR 80 as reference.

Figure S5: Forest plot of general population cohorts: HRs of AKI by age category; age 55–64, ACR 5 as reference.

Figure S6: Forest plot of general population cohorts: HRs of AKI at ACR 300 by age category; age 55–64, ACR 5 as reference.

Figure S7: Risk of AKI in CKD cohorts, by age and level of eGFR or ACR.

Figure S8: Forest plot of general population cohorts: HRs of AKI at eGFR 80 by sex.

Figure S9: Forest plot of general population cohorts: HRs of AKI at eGFR 45 by sex, men with eGFR 80 as reference.

Figure S10: Forest plot of general population cohorts: HRs of AKI at ACR 5 by sex.

Figure S11: Forest plot of general population cohorts: HRs of AKI at ACR 300 by sex, men with ACR 5 as reference.

Figure S12: Risk of AKI in CKD cohorts, by sex and level of eGFR or ACR.

Figure S13: Forest plot of general population cohorts: HRs of AKI at eGFR 80 by race.

Figure S14: Forest plot of general population cohorts: HRs of AKI at eGFR 45 by race; eGFR 80, white race as reference.

Figure S15: Forest plot of general population cohorts: HRs of AKI at ACR 5 by race.

Figure S16: Forest plot of general population cohorts: HRs of AKI at ACR 300 by race; ACR 5, white race as reference.

Figure S17: Risk of AKI in CKD cohorts, by race and level of eGFR or ACR.

Item S1: Data analysis overview and analytic notes for some studies.

Item S2: Acronyms or abbreviations for studies included and their key references.

Item S3: Acknowledgements and funding for collaborating cohorts.

Note: The supplementary material accompanying this article (doi:_____) is available at www.ajkd.org

Descriptive Text for Online Delivery of Supplementary Material

Supplementary Table S1 (PDF)

Characteristics of participating cohorts.

Supplementary Table S2 (PDF)

Adjusted HRs of AKI by category of eGFR and albuminuria across age among general population cohorts.

Supplementary Table S3 (PDF)

Adjusted HRs of AKI by category of eGFR and albuminuria across sex among general population cohorts.

Supplementary Table S4 (PDF)

Adjusted HRs of AKI by category of eGFR and albuminuria across race among general population cohorts.

Supplementary Figure S1 (PDF)

Adjusted HRs of AKI in general population cohorts.

Supplementary Figure S2 (PDF)

Adjusted HRs of AKI in CKD cohorts by level of eGFR and ACR.

Supplementary Figure S3 (PDF)

Forest plot of general population cohorts: HRs of AKI by age category; age 55–64, eGFR 80 as reference.

Supplementary Figure S4 (PDF)

Forest plot of general population cohorts: HRs of AKI at eGFR 45 by age category; age 55–64, eGFR 80 as reference.

Supplementary Figure S5 (PDF)

Forest plot of general population cohorts: HRs of AKI by age category; age 55–64, ACR 5 as reference.

Supplementary Figure S6 (PDF)

Forest plot of general population cohorts: HRs of AKI at ACR 300 by age category; age 55–64, ACR 5 as reference.

Supplementary Figure S7 (PDF)

Risk of AKI in CKD cohorts, by age and level of eGFR or ACR.

Supplementary Figure S8 (PDF)

Forest plot of general population cohorts: HRs of AKI at eGFR 80 by sex.

Supplementary Figure S9 (PDF)

Forest plot of general population cohorts: HRs of AKI at eGFR 45 by sex, men with eGFR 80 as reference.

Supplementary Figure S10 (PDF)

Forest plot of general population cohorts: HRs of AKI at ACR 5 by sex.

Supplementary Figure S11 (PDF)

Forest plot of general population cohorts: HRs of AKI at ACR 300 by sex, men with ACR 5 as reference.

Supplementary Figure S12 (PDF)

Risk of AKI in CKD cohorts, by sex and level of eGFR or ACR.

Supplementary Figure S13 (PDF)

Forest plot of general population cohorts: HRs of AKI at eGFR 80 by race.

Supplementary Figure S14 (PDF)

Forest plot of general population cohorts: HRs of AKI at eGFR 45 by race; eGFR 80, white race as reference.

Supplementary Figure S15 (PDF)

Forest plot of general population cohorts: HRs of AKI at ACR 5 by race.

Supplementary Figure S16 (PDF)

Forest plot of general population cohorts: HRs of AKI at ACR 300 by race; ACR 5, white race as reference.

Supplementary Figure S17 (PDF)

Risk of AKI in CKD cohorts, by race and level of eGFR or ACR.

Supplementary Item S1 (PDF)

Data analysis overview and analytic notes for some studies.

Supplementary Item S2 (PDF)

Acronyms or abbreviations for studies included and their key references.

Supplementary Item S3 (PDF)

Acknowledgements and funding for collaborating cohorts.

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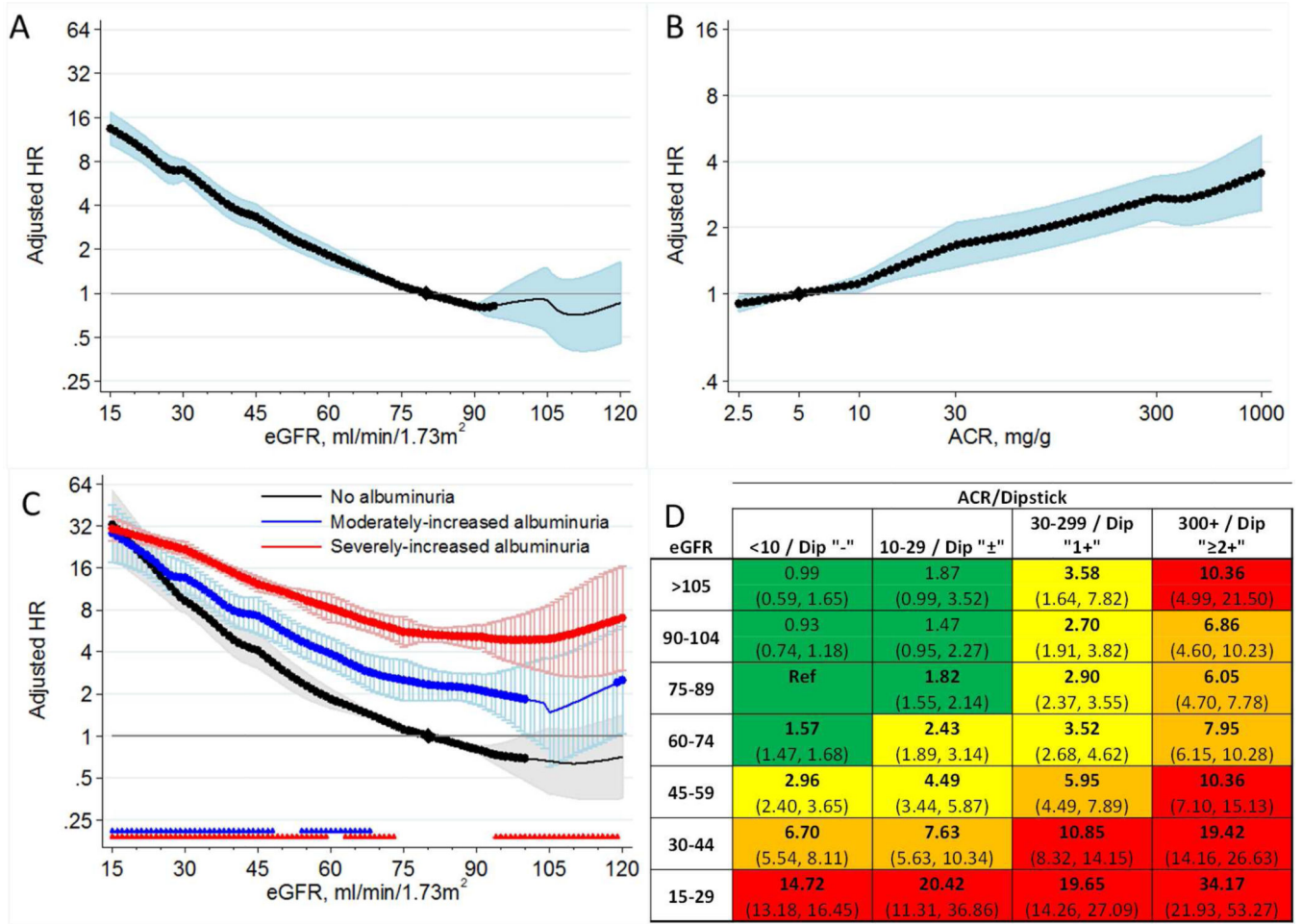


FIGURE 1. Adjusted hazard ratios of acute kidney injury in the general population cohorts by level of estimated glomerular filtration rate (eGFR) and albuminuria in continuous (panels A, B, and C) and categorical (panel D) analysis. In the panel C, bold lines indicate statistical significance compared to the reference (black diamond) at eGFR 80 ml/min/1.73 m² in the no albuminuria group, defined as urine albumin-creatinine (ACR) <30 mg/g or urine protein dipstick <1+. Stars along the x-axis represent significant pointwise interactions: the relative risk associated with a particular category of albuminuria compared to the no albuminuria category at that value of eGFR is significantly different than the corresponding relative risk seen at eGFR 80 ml/min/1.73 m². A graph without stars would reflect parallel risk associations. Hazard ratios (HRs) are derived from meta-analyses of the general population cohorts and are adjusted for sex, race, body mass index, systolic blood pressure, total cholesterol, history of cardiovascular disease, diabetes, and smoking status. The tables represents adjusted HRs derived from categorical analysis of the general population cohorts, with bold font representing statistical significance, and color coding by risk quartile.

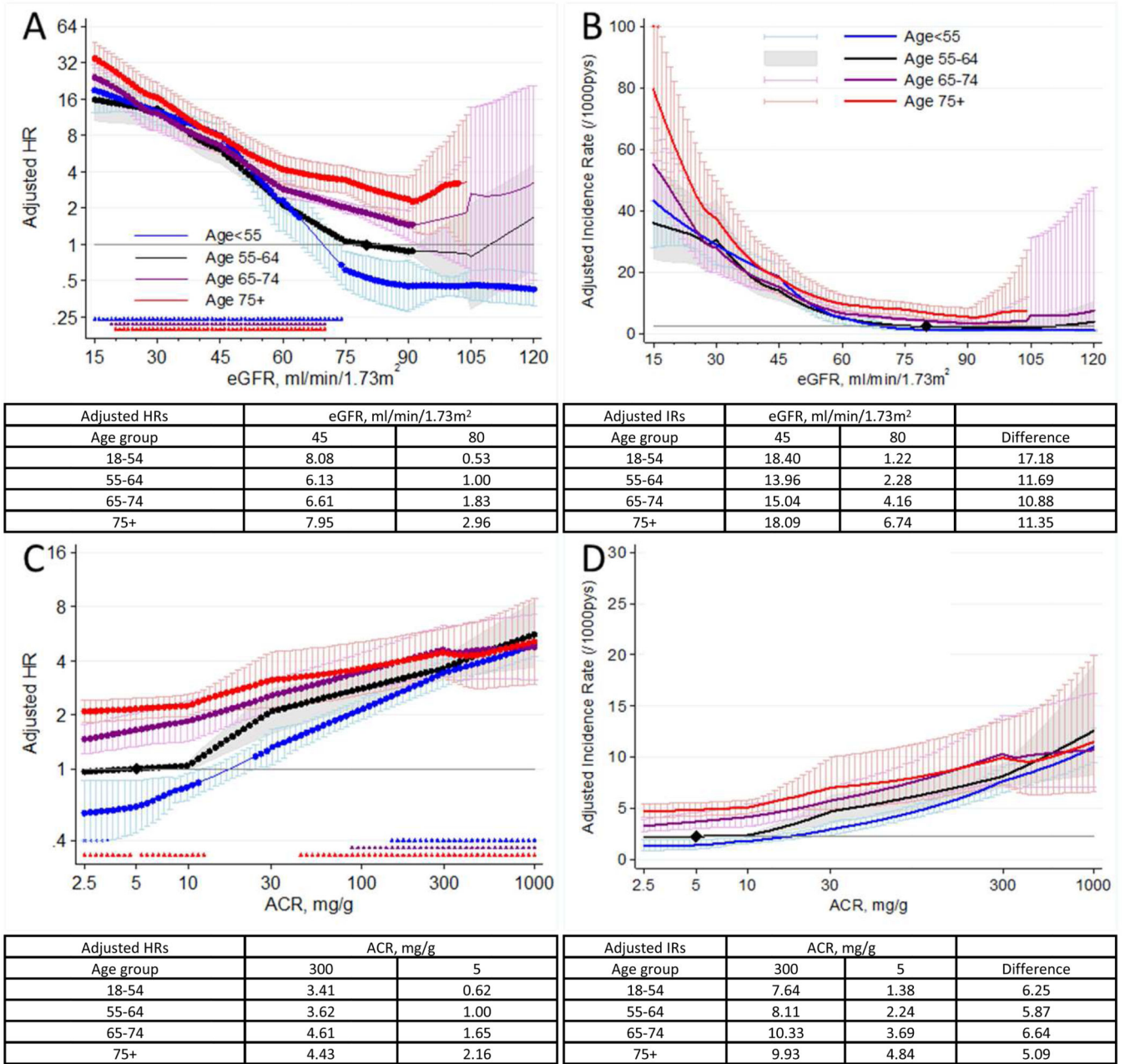


FIGURE 2.

Adjusted hazard ratios (panel A and C) and incidence rates (panel B and D) of acute kidney injury in the general population cohorts by level of estimated glomerular filtration rate and urine albumin-creatinine ratio (ACR), within categories of age. In the panels on the left, bold lines indicate statistical significance compared to the reference (black diamond) at estimated glomerular filtration rate (eGFR) 80 ml/min/1.73 m² or urine ACR 5 mg/g in ages 55–64 years. Stars along the x-axis represent significant pointwise interactions: the relative risk associated with a particular age category compared to the age category 55–64 years at that value of eGFR or ACR is significantly different than the corresponding relative risk seen at eGFR 80 ml/min/1.73 m² or ACR 5 mg/g. A graph without stars would reflect parallel risk

associations. Hazard ratios (HRs) are derived from meta-analyses of the general population cohorts and are adjusted for sex, race, body mass index, systolic blood pressure, total cholesterol, history of cardiovascular disease, diabetes, smoking status, and albuminuria. Tables represent adjusted HRs at eGFR 45 and 80 ml/min/1.73 m² and ACR 300 and 5 mg/g. In the panels on the right, lines and tables depict incidence rates (IRs) per 1,000 person-years, adjusted for the same covariates.

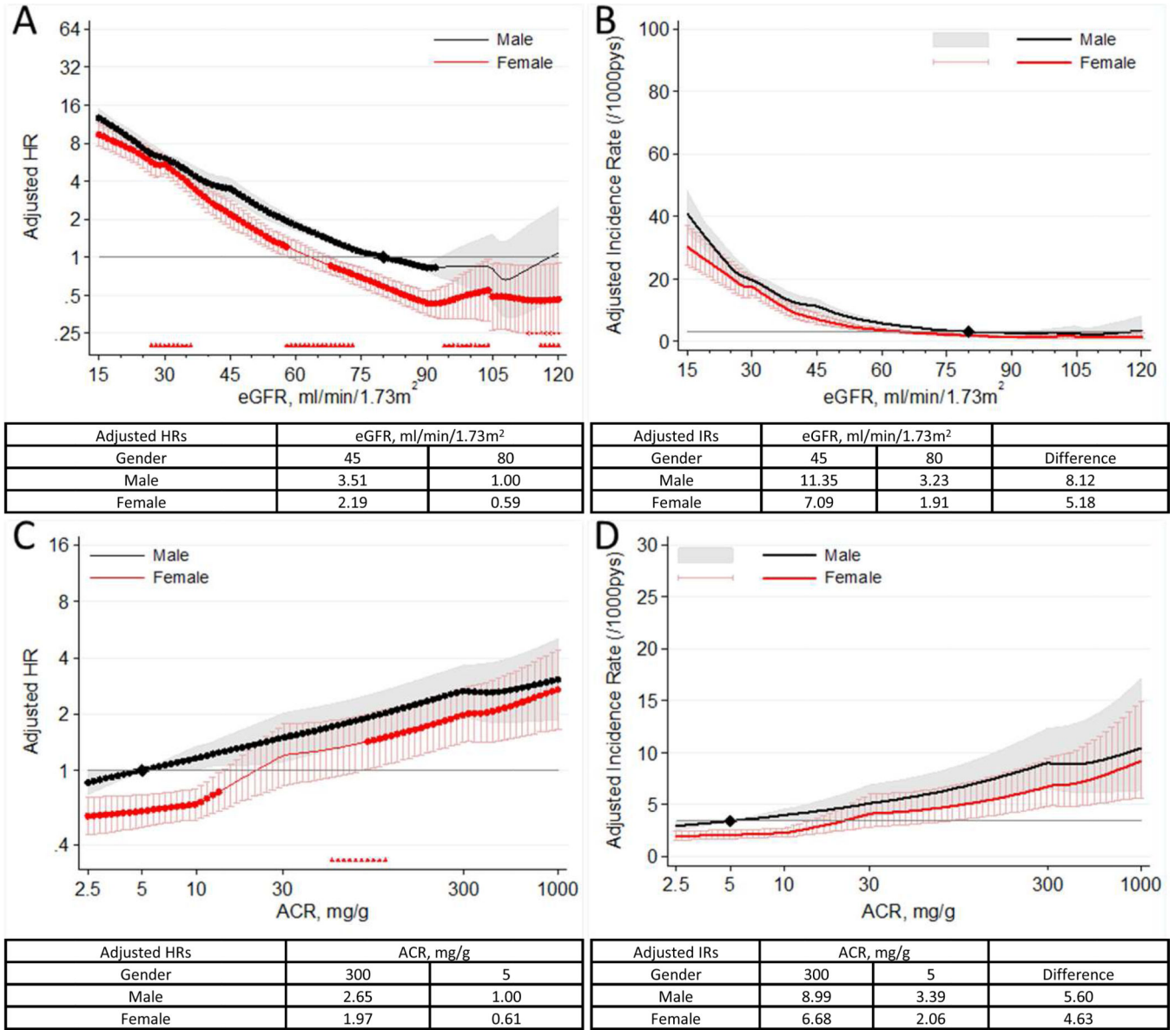


FIGURE 3. Adjusted hazard ratios (panel A and C) and incidence rates (panel B and D) of acute kidney injury in the general population cohorts by level of estimated glomerular filtration rate (eGFR) and urine albumin-creatinine ratio (ACR), within categories of sex. In the panels on the left, bold lines indicate statistical significance compared to the reference (black diamond) at eGFR 80 ml/min/1.73 m² or urine ACR 5 mg/g in men. Stars along the x-axis represent significant pointwise interactions: the relative risk in women compared to men at that value of eGFR or ACR is significantly different than the corresponding relative risk seen at eGFR 80 ml/min/1.73 m² or ACR 5 mg/g. Hazard ratios (HRs) are derived from meta-analyses of the general population cohorts and are adjusted for age, race, body mass index, systolic blood pressure, total cholesterol, history of cardiovascular disease, diabetes, smoking status, and albuminuria. Tables represent adjusted HRs at eGFR 45 and 80 ml/min/

1.73 m² and ACR 300 and 5 mg/g. In the panels on the right, lines and tables depict incidence rates (IRs) per 1,000 person-years, adjusted for the same covariates.

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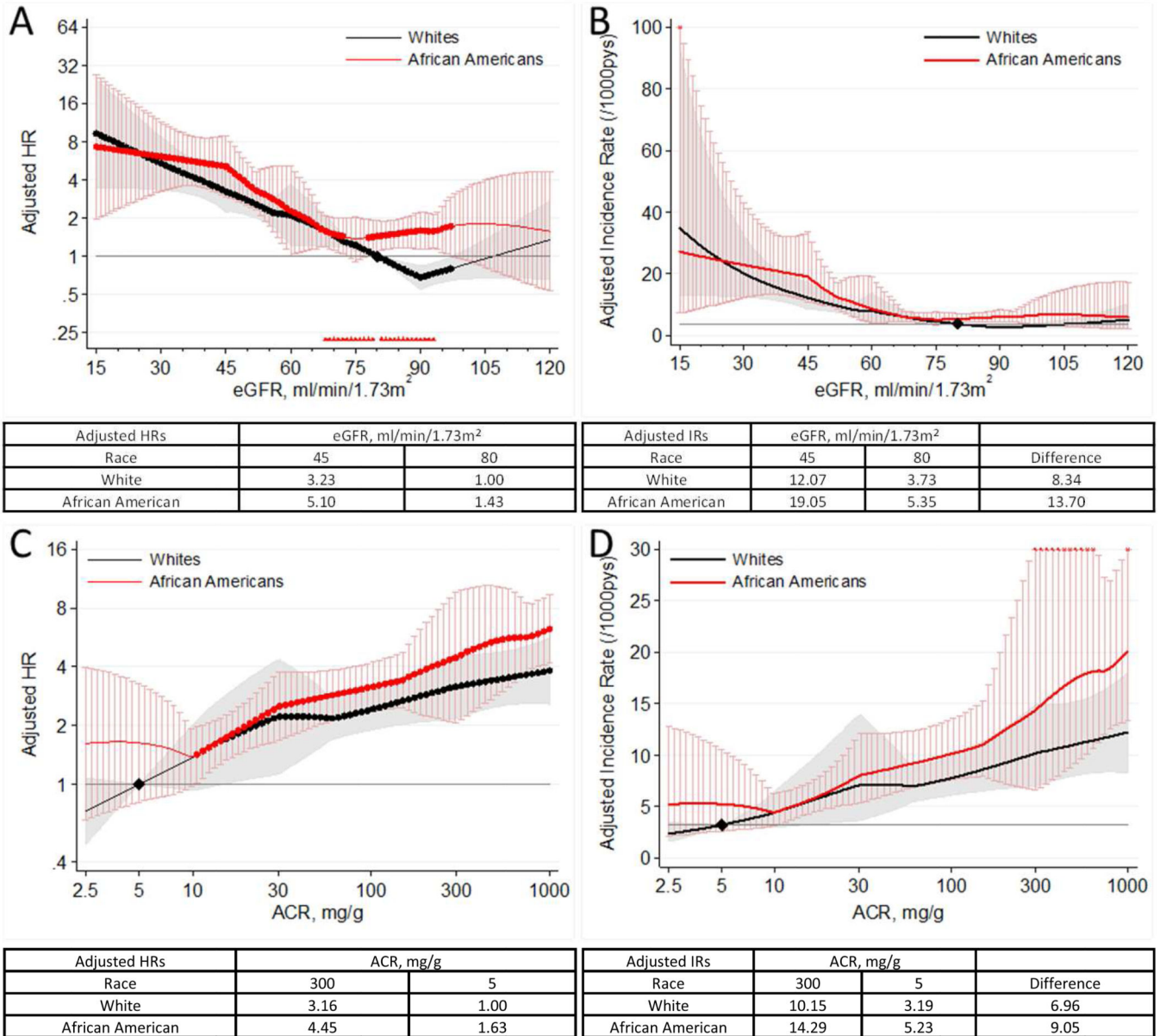


FIGURE 4. Adjusted hazard ratios (panel A and C) and incidence rates (panel B and D) of acute kidney injury in the general population cohorts by level of estimated glomerular filtration rate (eGFR) and urine albumin-creatinine ratio (ACR), within categories of race. In the panels on the left, bold lines indicate statistical significance compared to the reference (black diamond) at eGFR 80 ml/min/1.73 m² or urine ACR 5 mg/g in whites. Stars along the x-axis represent significant pointwise interactions: the relative risk in African Americans compared to whites at that value of eGFR or ACR is significantly different than the corresponding relative risk seen at eGFR 80 ml/min/1.73 m² or ACR 5 mg/g. Hazard ratios (HRs) are derived from meta-analyses of the general population cohorts and are adjusted for age, sex, body mass index, systolic blood pressure, total cholesterol, history of cardiovascular disease, diabetes, smoking status, and albuminuria. Tables represent adjusted HRs at eGFR 45 and

80 ml/min/1.73 m² and ACR 300 and 5 mg/g. In the panels on the right, lines and tables depict incidence rates (IRs) per 1,000 person-years, adjusted for the same covariates.

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Table 1

Characteristics of participating cohorts by AKI status

Study	Region	N	AKI Cases	F/U(y)	eGFR (ml/min/1.73 m ²) ^{***}	Albuminuria ^{†,***}	Age (y) ^{**}	Female ^{***}	African American ^{***}
General Population Cohorts									
AKDN	CA	920,686	9,060 (1%)	4 ± 2	64 ± 26 93 ± 20	23% 4%	68 ± 15 47 ± 16	45% 55%	0% 0%
ARIC*	US	11,424	655 (6%)	10 ± 2	77 ± 20 85 ± 15	25% 7%	65 ± 6 63 ± 6	47% 56%	30% 22%
CHS*	US	2,968	115 (4%)	9 ± 4	66 ± 19 72 ± 17	30% 20%	78 ± 5 78 ± 5	50% 59%	29% 16%
HUNT*	NO	9,670	281 (3%)	13 ± 2	73 ± 19 85 ± 20	28% 12%	71 ± 9 62 ± 15	44% 56%	0% 0%
Maccabi	IL	265,800	6,112 (2%)	4 ± 2	59 ± 21 87 ± 20	48% 14%	69 ± 12 57 ± 14	38% 50%	0% 0%
PREVEND*	NL	8,377	54 (1%)	10 ± 2	76 ± 17 84 ± 15	24% 11%	61 ± 11 49 ± 13	35% 50%	0% 1%
Severance	KR	65,021	151 (0.2%)	11 ± 3	75 ± 18 85 ± 16	16% 5%	58 ± 11 46 ± 12	40% 48%	0% 0%
ULSAM*	SE	1,103	52 (5%)	12 ± 4	70 ± 14 76 ± 10	23% 16%	71 ± 1 71 ± 1	0% 0%	0% 0%
Overall		1,285,049	16,480 (1%)	4 ± 3	63 ± 24 91 ± 20	32% 7%	69 ± 14 49 ± 16	42% 53%	1% 0%
CKD Cohorts									
CRIB*	UK	207	51 (25%)	5 ± 3	22 ± 6 28 ± 9	94% 76%	58 ± 15 63 ± 14	41% 26%	4% 6%
Geisinger ACR*	US	4,043	561 (14%)	4 ± 2	51 ± 9 52 ± 7	55% 41%	68 ± 10 69 ± 9	44% 54%	2% 2%
Geisinger Dip	US	920	185 (20%)	3 ± 2	47 ± 11 50 ± 9	53% 34%	65 ± 13 69 ± 11	45% 50%	1% 2%
KPNW	US	1,624	51 (3%)	4 ± 2	42 ± 13 47 ± 11	41% 31%	70 ± 10 72 ± 10	63% 56%	6% 3%
Sunnybrook*	CA	1,994	51 (3%)	3 ± 2	43 ± 26 68 ± 32	86% 60%	65 ± 17 59 ± 18	35% 48%	0% 0%
VA CKD*	US	70,731	1,188 (2%)	0.7 ± 0.5	55 ± 20 64 ± 21	59% 56%	70 ± 10 71 ± 10	2% 2%	16% 12%

Study	Region	N	AKI Cases	F/U(y)	eGFR (ml/min/1.73 m ²)**	Albuminuria [†] **	Age (y)**	Female**	African American**
Overall		79,519	2,087 (3%)	1 ± 1	51 ± 17 63 ± 21	58% 54%	68 ± 11 70 ± 11	22% 7%	10% 11%

Note: Unless otherwise indicated, values are given as mean ± standard deviation. See Item S2 for reference citations for studies.

AKDN, Alberta Kidney Disease Network; AKI, acute kidney injury; ARIC, Atherosclerosis Risk in Communities Study; CA, Canada; CHS, Cardiovascular Health Study; CKD, Chronic Kidney Disease; CRIB, Chronic Renal Impairment in Birmingham; eGFR, estimated glomerular filtration rate; F/U, follow-up; Geisinger CKD Study; HUNT, Nord Trøndelag Health Study; IL, Israel; KPNW, Kaiser Permanente Northwest; KR, Republic of Korea; NL, Netherlands; NO, Norway; PREVENT, Prevention of Renal and Vascular End-stage Disease; SE, Sweden; Severance, Severance Cohort Study; ULSAM, Uppsala Longitudinal Study of Adult Men; VA CKD, Veterans Affairs CKD Study; UK, United Kingdom; US, United States;

* Studies with albumin-creatinine ratio

[†] Proportion of participants with albumin-creatinine ratio > 30 mg/g or protein-creatinine ratio > 50 mg/g or dipstick protein 1+.

** Top value is for participants with AKI, bottom value is for participants without AKI.